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Prognostic Factors in Differentiated Thyroid Carcinoma: A Multivariate Analysis of 234 Consecutive Patients

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Background and Objectives: The clinical characteristics and patient outcome of a group of patients treated for differentiated thyroid carcinoma (DTC) were analyzed in order to assess the relative influence of different prognostic factors.
Materials and Methods: We retrospectively reviewed data about sex, age, size and histologic behavior of the tumor, extrathyroid extension of the tumor, lymph node status, distant metastasis at diagnosis, surgical procedures, and overall survival from 234 patients treated for DTC. Data were submitted to a statistical analysis.
Results: Using a univariate analysis, we found that survival rates were significantly influenced by age ($P = 0.0001$), size ($P = 0.018$), extrathyroidal extension ($P = 0.000001$), lymph node involvement ($P = 0.03$), and distant metastases ($P = 0.049$). Age and size were independent prognostic factors at multivariate analysis ($t = 2.694$ and $t = 2.443$, respectively).
Conclusions: On the basis of our results and of a review of the literature, we conclude that total thyroidectomy is the treatment of choice in DTC, except for small (<1 cm) papillary carcinoma, that could be treated by lobectomy plus isthmectomy, while lymphadenectomy is indicated only in case of macroscopic involvement.
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KEY WORDS: differentiated thyroid carcinoma; prognostic factors; thyroid surgery

INTRODUCTION

Well-differentiated type tumors of the thyroid account for approximately 80% of all cases [1]. Prognosis of papillary and follicular carcinoma of the thyroid is generally influenced by age at diagnosis, sex, extent of tumor, lymph node involvement, cellular nuclear DNA content and treatment [2].

Surgical management of thyroid tumors is generally accepted as the first step and, in some cases, must be followed by radioactive iodine treatment of nodes or distant metastases [2]. Differentiated thyroid cancer occasionally exhibits an aggressive biologic behavior that may be fatal. Although these cases occur rarely, it is useful to differentiate them from the group of patients who, after resection, are highly unlikely to develop recurrent disease.

The aim of this study was to analyze clinical characteristics and patient outcome of a group of patients treated for differentiated thyroid carcinoma in order to assess the relative influence on prognosis of different prognostic factors.

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MATERIALS AND METHODS

At the Department of Surgery of the Catholic University of Rome, 268 patients have been treated for thyroid carcinoma from January 1968 to July 1997. Among them, 234 patients had differentiated thyroid tumors. Details of their initial presentation, therapy, and outcome were obtained from the medical records. We retrospectively reviewed data about sex, age, size and histologic behavior of the tumor, extrathyroid extension of the tumor, lymph node status, distant metastasis at diagnosis, surgical treatment, and overall survival.

All patients had undergone thyroid resection by a staff surgeon. The extent of the thyroid resections varied from total thyroidectomy, near-total thyroidectomy, subtotal thyroidectomy to lobo-isthmectomy. A few patients in whom lymph node involvement was present at clinical or intraoperative examination underwent lymphadenectomy (node picking, central lymphadenectomy, or modified radical neck dissection).

Tumor dimension was determined on the specimen; according to TNM classification, tumors were divided into four groups: T1 $\leqslant$ 1 cm confined to the thyroid; T2 >1 cm, confined to the thyroid; T3 >4 cm; and T4 for any dimension with extracapsular invasion. Extrathyroid extension was evaluated macroscopically at operation and/or microscopically according to the histological findings.

Tumors were classified as either papillary or follicular types without consideration of histological subtypes. Distant metastases at diagnosis were identified by means of radiological imaging or scintigraphic assays. All patients were postoperatively treated with a suppressive dosage of levothyroxine.

Data regarding survival were collected through follow-up clinical controls, by telephone, or, in some cases, from patients records or patient registries. Data were subjected to a univariate analysis of the actuarial survival (Kaplan-Meier). The log-rank test was used for the evaluation of statistical significance. The *P*-value was considered significant at $\leqslant$0.05 and was based on two-tailed tests. In order to evaluate the independence of the significant factors obtained in this way, a multivariate analysis according to the Cox method was performed.

RESULTS

At diagnosis, the mean age ± SD of the 234 patients (167 women, 67 men) was 47.61 ± 16.65 years ranging from 16 to 87. Total thyroidectomy was performed in 117/234 patients (50%), near-total thyroidectomy in 5/234 (2.1%), and subtotal thyroidectomy in 9/234 patients (3.8%). In 75/234 patients (32.1%) completion thyroidectomy followed a previous partial resection. In 28/234 (12%) patients, it was possible to perform a lobo-isthmectomy.

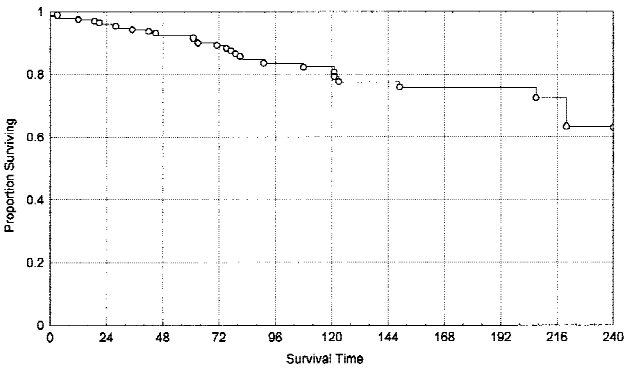

Fig. 1. Overall survival in a series of 234 consecutively observed patients with differentiated thyroid carcinoma.

Lymphadenectomy was carried out in 62/234 patients (26.5%): in 19/62 patients (30.7%) it was ''à la demande'' (node picking), while 34/62 patients (54.8%), underwent to central lymphadenectomy and 14.5% of patients (9/62) had a modified radical neck dissection.

Postoperative transient hypoparathyroidism rate was 6.4% (15/234), while permanent hypoparathyroidism was 2.6% (6/234). Transient recurrent laringeal nerve injury was 3.0% (7/234), and permanent nerve palsy was observed in 1.3% (3/234) of patients. Papillary carcinoma was found in 182/234 patients (77.8%), and follicular carcinoma in the remaining 52/234 (22.2%).

According to the TNM classification, 86/234 cases (36.8%) were classified as T1, 60/234 (25.6%) as T2, 34/234 (14.5%) as T3 and 54/234 (23.1%) as T4. In 19/62 (30.6%) of the patients who underwent lymphadenectomy (8.1% of the total), histological examination found lymph node metastasis.

Distant metastases were found in 3 of 234 patients (1.3%): lung metastases have been observed in two cases and bone metastasis in the other one. The median follow-up was 87.09 months (range: 1–340 months). Overall actuarial 10-year survival was 80.8%, while the 20-year survival rate was 63.3% (Fig. 1). If we do not consider deaths from causes other than thyroid cancer, the overall actuarial 10-year survival was 86.7%, while the 20-year survival rate was 70.6% (Fig. 2).

Univariate analysis shows the age at diagnosis, tumor size, nodes and distant metastasis, and extrathyroid extension to correlate significantly with survival (Table I).

Patients aged 45 years or older showed a shorter survival than did that of younger patients ($P = 0.0001$) (Fig. 3). Tumors $\leqslant$1 cm (T1) showed a better prognosis than that of T2–T4 tumors ($P = 0.018$) (Fig. 4). Extrathyroid extension correlated with a poor prognosis ($P = 0.000001$) (Fig. 5). Finally, survival was negatively influenced by the presence of nodes and/or distant metastases ($P = 0.03$, and $P = 0.049$ respectively) (Figs. 6 and 7, respectively).

Sex, surgical procedure, histology and lymphadenec-

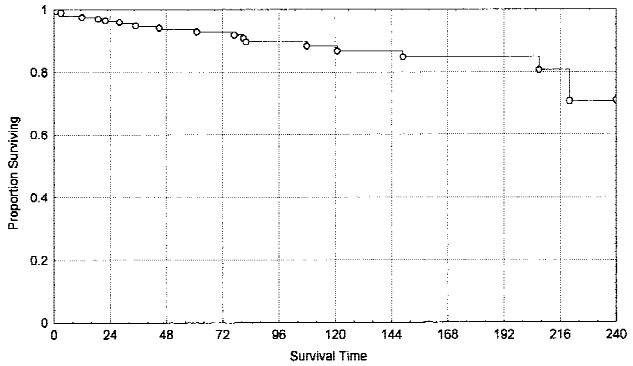

Fig. 2. Disease-free survival in a series of 234 consecutively observed patients with differentiated thyroid carcinoma.

TABLE I. Prognostic Factors for Differentiated Thyroid Carcinoma (DTC) According to Univariate Analysis

Factor	P[a]
Sex (male vs. female)	N.S. ($P = 0.26$)
Age (⩾45 yr vs. <45 yr)	0.0001
Histology (follicular vs. papillary)	N.S. ($P = 0.286$)
Size (T1 vs. T2–T4)	0.018
Extraglandular Invasion	0.000001
Lymph node status (N^+ vs. N^-)	0.03
Distant metastases	0.049
Surgical procedure (total thyroidectomy vs. other interventions)	N.S. ($P = 0.39$)
Lymphadenectomy	N.S. ($P = 0.7$)

[a]N.S., not statistical.

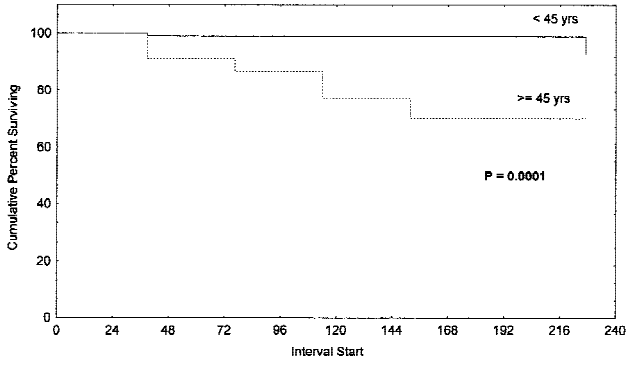

Fig. 3. Actuarial survival according to age. Patients younger than 45 years showed survival significantly ($P = 0.0001$) longer than patients aged 45 years or older.

tomy did not significantly influence the prognosis in our series ($P = 0.26$, $P = 0.39$, $P = 0.286$ and $P = 0.7$, respectively). Multivariate analysis showed that only age and tumor size had independent prognostic significance ($t = 2.694$ and $t = 2.443$) (Table II).

DISCUSSION

Despite the many reports concerning the diagnosis, treatment, and prognosis of differentiated thyroid carcinoma (DTC), there are still several controversies about the importance of the investigated prognostic factors in the different series that have been published [3]. Histology, extent of the primary tumor, lymph node involvement, presence of distant metastases, age, and sex have been investigated and related to the survival of the patients with DTC in previously published papers, but there is considerable disagreement regarding the relative im-

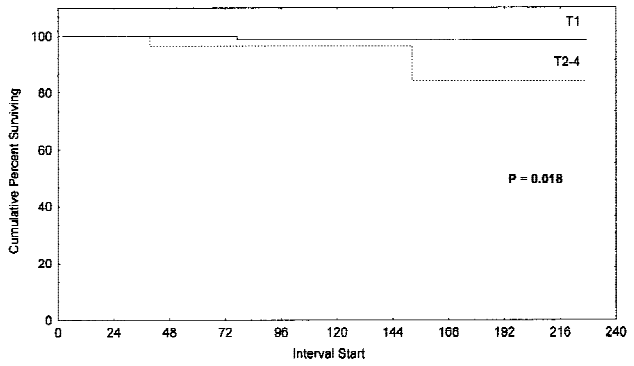

Fig. 4. Actuarial survival according to T (tumor size). Patients with T1 tumors showed survival significantly ($P = 0.018$) longer than patients with T2–T4 tumors.

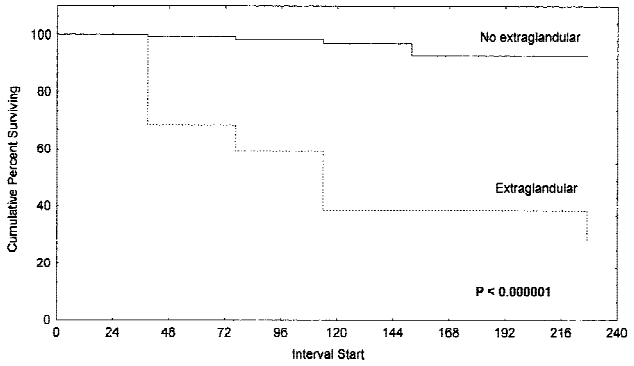

Fig. 5. Actuarial survival according to extraglandular extent. Patients with tumors confined to the thyroid showed survival significantly ($P = 0.000001$) longer than patients with extraglandular extension.

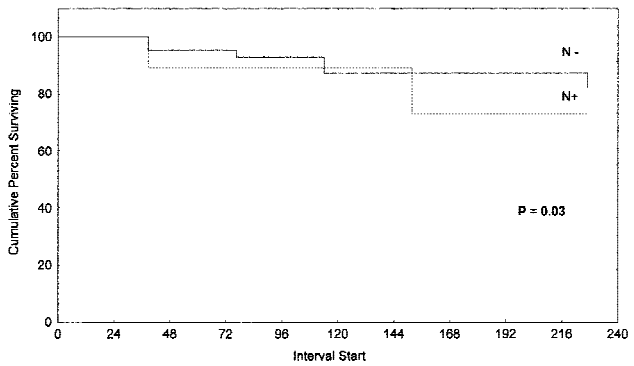

Fig. 6. Actuarial survival according to lymph node status. Patients without node metastases showed a survival significantly ($P = 0.03$) longer than patients with lymph node involvement.

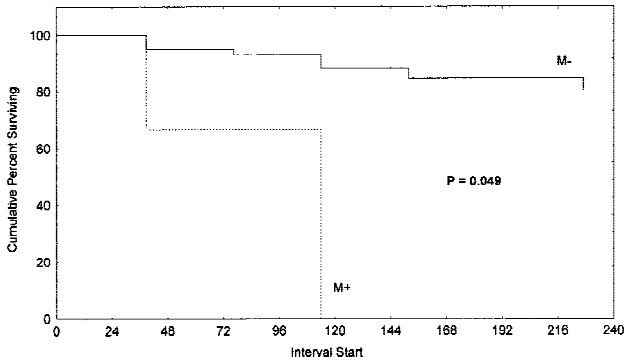

Fig. 7. Actuarial survival according to the presence of distant metastases. Patients without distant metastases showed a survival significantly ($P = 0.03$) longer than patients with distant metastases.

TABLE II. Prognostic Factors for 234 Cases of Differentiated Thyroid Carcinoma According to Multivariate Analysis

Factor	*t*
Age (⩾45 yr vs. <45 yr)	2.694
Size (T1 vs. T2–T4)	2.443
Extraglandular extension	0.224
Lymph node involvement	−0.145
Distant metastases	0.758

portance of these prognostic factors [3]. Moreover, many investigators have tried to identify those patients at risk of recurrence and/or death, by elaborating some score systems allowing classification of high and low risk patients with DTC, based on retrospective data [4–6].

In our series, the male-to-female ratio was 1:2.49, which was similar to that of previous reports [7–9]. It has been reported that female patients have better survival rates [10], and sex has been considered in the evaluation of some score systems [3,11]. Other studies reported that males with papillary carcinoma had a poorer prognosis at a univariate analysis, but gender was not statistically significant in multivariate analysis [7,12]. In the present study, sex was not a significant prognostic factor, although there was a slight tendency toward a higher mortality among men.

The significance of age at diagnosis as prognostic factor has been almost unanimously reported in the published studies [3,5–7,9,11]. Also in this series, age was significantly related to prognosis: patients older than 45 years had a higher mortality rate according to the multivariate analysis in this as well as in previously published studies [7,10,11].

In many papers, a correlation has been suggested between prognosis and histology, because of the supposed poorer prognosis of follicular carcinoma [3,6,8]. Conversely, many studies demonstrated no noteworthy difference in survival between papillary and follicular carcinoma [3,6]. In this series, we found no difference in the survival of patients with papillary and follicular carcinoma. Although not analyzed in this study, survival of patients with DTC has recently been correlated with histologic architecture in cases showing aggressive behavior, but not anaplastic transformation, and a new clinicopathologic entity of poorly differentiated thyroid carcinoma have been described [13,14]. However, the clinical value of histologic grading [3], as well as the significance of ploidy and DNA content [13] remains controversial. The stage (size, extent, lymph node involvement, distant metastases) of the tumor at diagnosis has been shown to be related to prognosis in all the published papers. Several studies have demonstrated the significance of the tumor size as prognostic factor at multivariate analysis, although there is still discrepancy about the cutoff size [8,15]. Hay et al. found a disease-related mortality among different groups of tumor size (2–4 cm, 4–7 cm, ⩾7 cm). We found that patients with T1 carcinoma had a better prognosis than the others: the size significance was independent at multivariate analysis.

Extracapsular extent of the tumor indicates more aggressive lesions; the mortality rate is similar in both microscopic and wide extrathyroidal invasion [16]. This feature is related to a high rate of lymph node and distant metastases, local recurrence, and disease-related death [6,9,16]. In our experience, extraglandular invasion is significantly related ($P = 0.000001$) to a poorer prognosis, although it was not an independent factor at multivariate analysis.

Lymph node metastases have been reported more frequently in papillary (37–88%) than in follicular (10%) thyroid carcinoma [3,6,9]. The prognostic significance of regional lymph node involvement remains controversial in both histologic types [17]. In our series, lymph node metastases were a negative prognostic factor, although not independent at a multivariate analysis, which is different from other reports [1,3,18,19].

Distant metastases at diagnosis, usually associated with the larger tumors [9], have been shown to be related to a poorer prognosis in DTC in almost all the published series [8,9,20]. The overall mortality rate for distant metastases could be lesser in patients who received aggressive postoperative radioiodine treatment [21]. We observed only three patients with distant metastasis at diagnosis (2 lung and 1 bone metastasis), with a poor prognosis.

Surgical procedure such as the extent of thyroidectomy and usefulness of lymphadenectomy for DTC remains controversial. Some investigators reported that patients treated with conservative surgery, such as lobectomy plus isthmectomy or subtotal thyroidectomy, have no poorer survival rates than those who had more aggressive treatment [15,22]. Conversely, other authors found that total thyroidectomy (TT) resulted in a lower recurrence rate and a longer disease-free survival

[1,6,8,16], without a high complication rate. In fact, the incidence of hypoparathyroidism or permanent recurrent laryngeal nerve palsy is reported to be less than 3% in skilled hands [23,24]. TT allows elimination of contralateral tumor foci: bilateral thyroid carcinoma has been reported in 30–88% of cases [24]. Furthermore, TT allows also a better postoperative follow-up, with total body iodine scintiscan and serum thyroglobulin (sTG) determination [21,24]. Finally, a more aggressive approach reduces the possibility of an anaplastic transformation of remnant DTC [23]. Thus, on the basis of data from previously published papers [9,15], we consider suitable a conservative approach only in the case of papillary carcinoma of ⩽1 cm (T1), in whom no difference in survival rate has been shown to be related to surgical procedure (lobectomy plus isthmectomy vs. TT). In the other patients, TT, near-total thyroidectomy, or completion thyroidectomy are mandatory. Some investigators believe lymphadenectomy is indicated in all cases, because of the high lymph node involvement rate and its prognostic significance. In our series, however, lymphadectomy was not found to influence prognosis significantly. We therefore maintain that lymphadenectomy should be performed only in cases of macroscopic involvement, because of the lack of usefulness in disease control in the other cases.

CONCLUSIONS

DTC has a good prognosis. At univariate analysis, we found that age, size and extent of the lesions, lymph node and distant metastases were related to a poorer prognosis. However, at multivariate analysis, only age and size were independent predictors of decreased survival.

It could be suggested that a more aggressive surgical approach may be suitable in patients older than 45 years and/or in tumors of >1 cm; moreover, also on the basis of previously published papers, it seems that a conservative procedure could be the treatment of choice in small (⩽1 cm) papillary carcinoma, while lymphadenectomy is indicated only in case of macroscopic nodal involvement.

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